Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/public/index_e.html

Unpublished supporting documentation for the health effects assessment, which presents additional information, is available upon request from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Sections of the Assessment Report and supporting documentation on genotoxicity and reproductive and developmental toxicity were reviewed by D. Blakey and W. Foster, respectively, of the Environmental and Occupational Toxicology Division of Health Canada. A review of the exposure assessment included in the critical epidemiological studies was prepared under contract by M. Gerin and J. Siemiatycki of the Institut Armand-Frappier, University of Quebec.

In the first stage of external review, sections of the supporting documentation pertaining to human health were considered by the following individuals, primarily to address adequacy of coverage: J. Aquavella, Monsanto Company; M. Bird, Exxon Biomedical Sciences, Inc.; J.A. Bond, Chemical Industry Institute of Toxicology; I. Brooke, United Kingdom Health and Safety Executive; G. Granville, Shell Canada Ltd.; R. Keefe, Imperial Oil Ltd.; A. Koppikar, US Environmental Protection Agency; R.J. Lewis, Exxon Biomedical Sciences, Inc.; K. Peltonen, Finnish Institute of Occupational Health; and F. Ratpan, Nova Chemicals

In the second stage of external review, accuracy of reporting, adequacy of coverage, and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered in written review by BIBRA International and the following individuals: R.J. Albertini, University of Vermont; J.A. Bond, Chemical Industry Institute of Toxicology; I. Brooke, United Kingdom Health and Safety Executive; J. Bucher, US National Toxicology Program; B. Davis, US National Toxicology Program; E. Delzell, University of Alabama at Birmingham; B.J. Divine, Texaco; A.A. Elfarra, University of Wisconsin-Madison; E. Frome, Oak Ridge National Laboratory; B.D. Goldstein, Environmental and Occupational Health Sciences Institute; R.F. Henderson, Lovelace Respiratory Research Institute; R.D. Irons, University of Colorado Health Sciences Center; A. Koppikar, US Environmental Protection Agency; J. Lubin, US National Cancer Institute; J. Lynch, Exxon Biomedical Sciences, Inc. (retired); R.L. Melnick, US National Toxicology Program; K. Peltonen, Finnish Institute of Occupational Health; A.G. Renwick, University of Southampton; J. Siemiatycki, Institut Armand-Frappier; L.T. Stayner, US National Institute for Occupational Safety and Health; J.A. Swenberg, University of North Carolina; R. Tice, Integrated Laboratory Systems, Inc.; and J.B. Ward, Jr., University of Texas Medical Branch.

In the third and final stage of external expert review, adequacy of incorporation of the comments received during the second stage was considered at a final meeting of a panel of the following members convened by Toxicology Excellence in Risk Assessment (TERA) in November 1998: H.

Clewell, K.S. Crump Division of ICF Kaiser; M.L. Dourson, TERA; and L. Erdreich, Bailey Research Associates, Inc.

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting. The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Concurrent with review of the draft CICAD, there was also a public comment period for the source national assessment, in which the Priority Substances List Assessment Report was made available for 60 days (2 October to 1 December 1999). A summary of the comments and responses is available on the Internet at www.ec.gc.cceb1/eng/public/index_e.html.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 1,3-butadiene was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

M. Baril, International Programme on Chemical Safety/ Institut de Recherche en Santé et en Sécurité du Travail du Québec, Canada

R. Benson, Drinking Water Program, US Environmental Protection Agency, USA

T. Berzins, National Chemicals Inspectorate (KEMI), Sweden

R. Cary, Health and Safety Executive, United Kingdom

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, USA

P. Edwards, Department of Health, United Kingdom

H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, USA

R. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

J. Heuer, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Germany

J. Jinot, US Environmental Protection Agency, USA

C. Kimmel, US Environmental Protection Agency, USA

A.M. Koppikar, US Environmental Protection Agency, USA

S. Kristensen, National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Australia

N. Moore, BP Amoco Chemicals (commented through Department of Health, United Kingdom)

H. Nagy, National Institute of Occupational Safety and Health, USA

S. Tarkowski, Nofer Institute of Occupational Medicine, Poland

L. Vodickova, National Institute of Public Health, Centre of Industrial Hygiene and Occupational Diseases, Czech Republic

P. Yao, Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, People's Republic of China

K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umvelt und Gesundheit, Germany (transmitted comments from BUA and industry representatives)

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Helsinki, Finland, 26–29 June 2000

Members

Mr H. Ahlers, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Dr R.M. Bruce, Office of Research and Development, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Mr R. Cary, Health and Safety Executive, Liverpool, United Kingdom *(Rapporteur)*

Dr R.S. Chhabra, General Toxicology Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Dr H. Choudhury, National Center for Environmental Assessment, US Environmental Protection Agency, Cincinnati, OH, USA

Dr S. Dobson, Centre for Ecology and Hydrology, Monks Wood, Abbots Ripton, United Kingdom *(Chairman)*

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany

Ms K. Hughes, Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr G. Koennecker, Chemical Risk Assessment, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr A. Nishikawa, Division of Pathology, Biological Safety Research Centre, National Institute of Health Sciences, Tokyo, Japan

Dr V. Riihimäki, Finnish Institute of Occupational Health, Helsinki, Finland

Dr J. Risher, Agency for Toxic Substances and Disease Registry, Division of Toxicology, US Department of Health and Human Services, Atlanta, GA, USA

Professor K. Savolainen, Finnish Institute of Occupational Health, Helsinki, Finland *(Vice-Chairman)*

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr S. Soliman, Department of Pesticide Chemistry, Faculty of Agriculture, Alexandria University, Alexandria, Egypt

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, NSW, Australia

Observer

Dr R.J. Lewis (representative of European Centre for Ecotoxicology and Toxicology of Chemicals), Epidemiology and Health Surveillance, ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland *(Secretary)*

Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Younes, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

APPENDIX 4 — QUANTITATION OF EXPOSURE — RESPONSE FOR CRITICAL EFFECTS ASSOCIATED WITH EXPOSURE TO 1,3-BUTADIENE

Tumorigenic concentrations based on epidemiological data

Methods

The raw study data[22] for the six plants investigated by Delzell et al. (1995) were used to calculate the potency estimates. The data consisted of the cumulative occupational exposures to butadiene and styrene at each year of each subject's life (person-year), beginning with his entry into the cohort and terminating with death or other exit from the cohort. The data also contained information on race, age, calendar year, and years since hire of each subject.

The response of interest was cases of death due to all forms of leukaemia, as information on the specific type of leukaemia was insufficient; only cases in which leukaemia was considered the underlying cause of death were considered in these analyses. Exposure estimates were cumulative occupational exposures in ppm-years assumed to be incurred for 8 h/day, 240 days/year over a 45-year working life.

The objective of this exposure–response analysis was to compute the carcinogenic potency, expressed as the TC_{01}, or the concentration of butadiene associated with a 1% excess probability of dying from leukaemia. This analysis involved two stages. First, the relationship between exposure and the death rate due to leukaemia within the cohort was modelled. This was accomplished by collapsing (or stratifying) the data into discrete exposure cate gories and then modelling the mean exposure in each category versus the death rates due to leukaemia. In the second stage of analysis, the TC_{01} was calculated based on this exposure–response relationship and the background mortality rates in the Canadian population.

Exposure–response modelling

In addition to stratifying by exposure, the data were stratified by race, age, calendar year, years since hire, and styrene exposure in order to incorporate this information into the exposure–response relationship. Each of these variables was collapsed into a small number of discrete categories in order to reduce the number of strata, thereby improving model stability. These variables and their categories are presented in Table A-1. Exposure, defined as the mean cumulative exposure per person-year, was calculated for person-years falling into each possible combination of the stratification variables.

Table A-1: Stratification variables for exposure–response modelling of epidemiological data from Delzell et al. (1995).

Variable	Categories
Cumulative butadiene exposure (ppm-years)	0, >0–4, 5–9, 10–19, 20–29, 30–49, 50–99, 100–199, 200+
Cumulative styrene exposure (ppm-years)	0, >0–3, 4–6, 7–9, 10–19, 20–39, 40–59, 60–79, 80+
Race	black, white, other
Age	40–44, 45–49, ..., 75–79, 80+
Calendar period	1940–44, 1945–49, ..., 1990–95
Years since hire	0–4, 5–9, ..., 50–55

The data were imported to Epicure (1993)[23] for exposure– response modelling. All fitted models were of the form:

$$RR = O/E = g(D(t))$$

where RR is the rate ratio, O and E are the observed and expected numbers of leukaemia deaths, $D(t)$ is cumulative butadiene expo sure up to time t, and g is the exposure–response model, which is constrained to pass through one at zero exposure. Four different models, discussed in more detail below, were fitted to the data. At the model-fitting stage, the expected number of deaths is calculated on the basis of the non-exposed person-years in the cohort, and not from population background rates.

Lifetime probability of death due to leukaemia

Once the fitted exposure–response model was obtained, the lifetime probability of death due to leukaemia was computed using lifetable methods taking into account the death rates in the Cana dian population. The derivation of the formula used for the lifetime probability of death due to leukaemia

proceeds as follows.

Let d(t) represent the exposure concentration of butadiene in ppm at age t years, and let D(t) denote the cumulative exposure in ppm-years, with:

$$D(t) = \int_0^t d(x)\,dx$$

This formulation of cumulative exposure allows for the possibility of non-constant exposure scenarios.

At a cumulative exposure of D(t) ppm-years, the probability of dying from leukaemia by age t is given by:

$$P(D(t);t) = \int_0^t h_R(D(x);x)\,S(x)\,dx \qquad (1)$$

where $h_R(D(t);t)$ is the mortality rate from leukaemia at age t given a cumulative exposure to butadiene of D(t), and S(t) is the probability of survival up to age t. Equation (1) follows from the argument that the probability of death by age t is equal to the probability of death at age t multiplied by the probability of surviving up until age t. In lifetable analysis, the mortality and survival rates are constant for each year, so the integral in (1) can be replaced by a summation over year.

Exposure to butadiene is assumed to augment the back ground rate of leukaemia in a multiplicative fashion. In other words, the mortality rate, given exposure to butadiene, is equal to the background exposure rate multiplied by the excess risk due to exposure to butadiene. This is known as the "proportional hazard" model and is expressed as:

$$H_R(D(t);t) = h(t) \times [g(D(t))] \qquad (2)$$

where $h(t)$ is the background mortality rate from leukaemia in the population, calculated from Canadian age-specific death rates[24] due to leukaemia, and g(D(t)) is the fitted exposure–response model, or excess risk at age t.

The survival rate, S(t), appearing in equation (1) is computed from Canadian age-specific death rates due to all causes, where the reported Canadian leukaemia mortality rate is replaced by the modelled rate in order to incorporate exposure to butadiene. The formula describing the probability of survival up to age i is given by:

$$S_i = \exp\left[-\sum_{j=1}^{i} h_j^* - h_j + h_j g_j\right] \qquad (3)$$

where h_j^* and h_j are the Canadian mortality rates due to all causes and due to leukaemia at age j, respectively, and $g_j = g(D(j))$ is the excess risk at age j.

Substituting equation (2) into (1), the lifetime probability of death due to leukaemia is given by:

$$P(D(70);70) = \sum_{i=1}^{70} h_i g_i S_{i-1}$$

where 1–70 years is the standard lifetime for a human.

Cancer potency (TC_{01})

The TC_{01} is computed by determining the exposure D(t) at which the excess risk is equal to 0.01. That is,

$$\frac{P(D(t);t) - P(0;t)}{1 - P(0;t)} = 0.01$$

If a constant exposure d is assumed for an individual from birth to age 70 years, then $d(t) = d$ ppm and the cumulative exposure $D(t) = d \times t$ ppm-years. The TC_{01} is then the ambient exposure level d (in ppm) at which the excess risk equals 0.01 at $t = 70$ years.

Lagged exposure analysis

In separate analyses, exposures were lagged by $n = 2$, 5, 10, 15, 20, and 25 years to determine if the models would provide better fits if the most recent n years of exposure were ignored. An n-year lag was achieved by resetting an individual's cumulative exposure at each year to be equal to the exposure he had accumulated n years prior. In so doing, the last n years of exposure do not affect the probability of developing leukaemia. The data were first stratified on unlagged cumulative exposure, and then the individual exposures were lagged. Thus, the number of strata remains constant when using different lag periods, and models with different lags may be directly compared (Preston et al., 1987).

Validation study

To assess the predictive power of the exposure–response models, a validation study was performed in which individuals in the cohort were divided randomly into two groups. The models were fit separately to both groups, and then a likelihood ratio test was performed to determine if the estimated parameters were equal. The process of dividing and fitting was repeated 1000 times to characterize the variability due to the random splitting process. If the models provided consistent fits, then the likelihood ratio test would be expected to reject at a rate equal to the desired signif icance level of the test (i.e., at a significance level of 0.05, the fitted parameters should be significantly different 1 in 20 times). If the tests are significant more often than this, the confidence in the predictive power of the models is reduced.

Results

Exposure–response modelling

Four different exposure–response models were examined and are presented in Table A-2. These models are identical to those fitted in the Delzell et al. (1995) report except that model 2 is more general and flexible than the square root model used by those authors. Preliminary analysis indicated that all stratification vari ables except race significantly affected the model fit. Since race was only marginally insignificant, all variables were used to stratify the data prior to model fitting.

The four models were fitted while stratifying on race, age, calendar year, years since hire, and styrene exposure. The results of the model fitting are displayed in Table A-2. (Note: A smaller deviance roughly indicates a better fit.) A graphic representation of the data and the fitted models is shown in Figure A-1. Judging from the model deviances and the shape of the curves relative to the data, especially in the low-dose region, model 1 provides the best fit to the data.

For purposes of comparison, the same models were fitted using the median exposure as per the Delzell et al. (1995) report. These analyses indicated that there is little difference between using mean or median exposures. Models including age as a multiplying factor of $e^{gamma \cdot age}$ instead of as a stratification variable were also fitted, but these models did not fit as well. Since cumulative exposure and years since hire may be confounded, their interaction was examined. The interaction was not significant for any of the models. The same models were refitted excluding the largest exposure group (200+ ppm-years), but this did not significantly affect any of the parameter estimates. The four models were also refitted allowing for different background rates for control and exposed populations. Different background rates might be neces sary in occupational studies where lifetime non-exposed workers may differ fundamentally from exposed workers as a result of differences in jobs and work areas. Results of this analysis indicated that different background rates are not necessary for these data.

The parameter estimates obtained in the present analysis are also not significantly different from those presented in the Delzell et al. (1995) report. The differences in parameter estimates are likely due to the different levels used in the stratification vari ables. Table A-2 compares the parameter estimates obtained in this analysis with those of the Delzell et al. (1995) report.

Cancer potency (TC_{01})

The TC_{01}s were calculated for each model using the lifetable methods described above, and the resulting ambient occupational exposures per person-year were converted to environmental exposures by assuming that the exposures occurred for 8 h/day,

Table A-2: Parameter estimates and model deviances for each of four models fit to mean cumulative exposure per person-year for Delzell et al. (1995) study and comparison with parameter estimates from Delzell et al. (1995) analyses.

Model	Parameter estimates	Standard error	Deviance	Parameter estimates from Delzell et al. (1995) study	*p*-value[a]
1) RR = (1 + dose)	*alpha* = 0.2850	SE(*alpha*) = 0.0976	171.5	*alpha* = 0.2028	0.39
2) RR = 1 + *beta*•dose	*alpha* = 0.3999 *beta* = 0.4558	SE(*alpha*) = 0.2733 SE(*beta*) = 0.8222	172.0	*alpha* = 0.5000[b] *beta* = 0.1293	0.62
3) RR = $e^{gamma \cdot dose}$	*beta* = 0.0029	SE(*beta*) = 0.0014	176.7	*beta* = 0.0041	0.38
4) RR = 1 + *beta*•dose	*beta* = 0.0099	SE(*beta*) = 0.0065	174.7	*beta* = 0.0068	0.63

[a] *p*-value of likelihood ratio test of equality of parameters.

[b] For the Delzell et al. (1995) analysis, *alpha* was fixed at 0.5, and only *beta* was estimated.

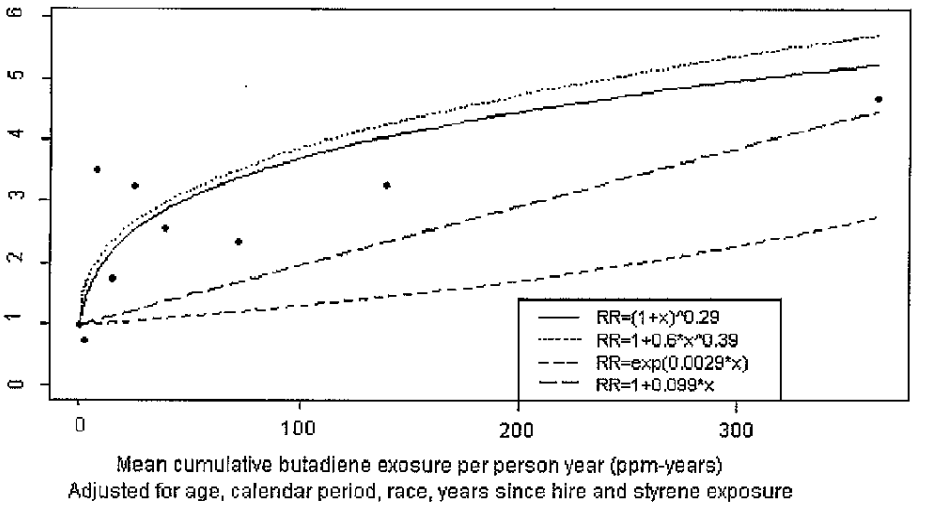


Figure A-1. Observed rate ratios and fitted curves for leukaemia in Delzell et al. (1995) study.

240 days/year. This amounts to multiplying the TC_{01} by:

$$\frac{8\ h}{24\ h} \times \frac{240\ days}{365\ days}$$

To convert the ambient exposures from ppm to mg/m^3, the TC_{01}s are further multiplied by 2.21, the conversion factor for butadiene. The occupational and equivalent environmental TC_{01}s are presented in Table A-3. Environmental TC_{01}s for each of the four models ranged from 1.4 to 4.3 mg/m^3. TC_{01}s calculated excluding the largest exposure group were slightly smaller, ranging from 0.6 to 1.6 mg/m^3, while those calculated on the basis of median exposures were similar, ranging from 0.4 to 5.0 mg/m^3.

TC_{01}s were also calculated using the parameter estimates from the Delzell et al. (1995) report and are compared with the TC_{01}s developed here in Table A-3. They ranged from 3.1 to 14.3 mg/m^3.

Lagged exposure analysis

The same four models were fitted when exposures were lagged by 2, 5, 10, 15, 20, and 25 years. The resulting model fits are displayed in Table A-4. Since the deviances are similar for each lag period, this analysis indicates that lagging exposures does not dramatically improve the fit of any of the four models. In fact, TC_{01}s for all four models and all lag periods ranged from 0.8 to 4.3 mg/m^3.

Validation study

With respect to model validation, the *p*-values for the tests of equality of the parameters are displayed in Table A-5. If the models were providing consistent fits between the two halves, the propor tion of *p*-values less than the significance level of *alpha* would be *alpha*. The results of the simulation study indicate that the test is rejecting more often than would be expected if the models

were providing the same fits to both halves of the data. For model 1, the test was rejected at a significance level of 1% in 7.4% of the runs, whereas a rejection rate of 1% of the runs would be expected if the model was fitting consistently. The results of this analysis reduce the confidence in the power of the models to predict leukaemia mortality rates.

Table A-3: Carcinogenic potency estimates (TC_{01}s) for models fit to mean cumulative exposure per person-year based on Delzell et al. (1995) study and comparison with estimates from Delzell et al. (1995) analyses.

Model	Current analysis		Delzell et al. (1995) analysis
	Occupational TC_{01} (mg/m^3)	Environmental TC_{01} (mg/m^3)	Environmental TC_{01} (mg/m^3)
1) RR = (1 + dose)	7.8	1.7	14.3
2) RR = 1 + *beta*•dose	6.5	1.4	6.4
3) RR = $e^{beta \cdot dose}$	19.8	4.3	3.1
4) RR = 1 + *beta*•dose	13.8	3.0	4.5

Summary

It is noteworthy that the choice of the exposure–response model does not have a large impact on the resulting TC_{01}; as indicated in Table A-3, the values are similar, ranging from 1.4 to 4.3 mg/m^3. However, if a best model must be chosen, it would be

model 1, owing to the smaller deviance (Table A-2), the shape of the curve relative to the data in the low-dose region (Figure A-1), and the fact that it has one fewer parameter than model 2, which provides a similar fit. The TC_{01} for model 1 is 1.7 mg/m^3.

It is difficult, though, to assess how well any of these models truly describes the data. It is noted that the plot in Figure A-1 provides only a rough indication of the shape of the data, since each point on the plot is an average of data in many strata. The results of the validation study reduce confidence in the ability of the models to predict leukaemia mortality.

The choice of exposure lag does not greatly improve the fit of any of the four models, and it does not affect the resulting TC_{01}. Including all lagged models, the range of TC_{01}s is still from 0.8 to 4.3 mg/m^3.

For comparison with these values, potency estimates were also calculated on the basis of the recent case–control study of styrene-butadiene rubber workers by Matanoski et al. (1997). Although workers were from plants subsumed in the Delzell et al. (1995) study, exposure was independently characterized. Treating the odds ratio presented by these authors as a rate ratio (since leukaemia is a rare disease) and using their model and parameter estimates as well as the same lifetable methods described above, the TC_{01} for environmental exposure was calculated to be 0.4 mg/m^3. It is reassuring, therefore, that this value is only slightly lower than the estimates derived on the basis of the Delzell et al. (1995) cohort study data.

Tumorigenic concentrations based on data from studies in experimental animals

Estimates of carcinogenic potency were calculated on the basis of the incidences of malignant lymphomas, histiocytic sarcomas, cardiac haemangiosarcomas, alveolar/bronchiolar adenomas or carcinomas, hepatocellular adenomas or carcinomas, squamous cell papillomas or carcinomas of the forestomach, adenomas or carcinomas of the Harderian gland, granulosa cell tumours of the ovaries, and adenoacanthomas, carcinomas, or malignant mixed tumours of the mammary gland observed in B6C3F$_1$ mice in the chronic bioassay conducted by the NTP (1993) and the mammary gland tumours, pancreatic exocrine adenomas, Leydig cell tumours, Zymbal gland carcinomas, thyroid follicular cell adenomas or carcinomas, and uterine sarcomas in Sprague-Dawley rats reported by Hazleton Laboratories Europe Ltd. (1981a). (The tumour incidence data for each of the sites considered are presented in Tables 2 and 3.)

In the NTP study, mice were exposed to 0, 6.25, 20, 62.5, 200, or 625 ppm (0, 13.8, 44.2, 138, 442, or 1383 mg/m^3) butadiene for 6 h/day, 5 days/week, for 103 weeks. Survival of mice decreased with increasing exposure concentration; therefore, to minimize the effect of the high mortality rate, the poly-3 adjusted data (Bailer & Portier, 1988; Portier & Bailer, 1989) presented in the NTP (1993) report were used in these calculations. For some tumour types, the adjusted data still demonstrated downward curvature at the highest concentration. In these cases, the high- exposure group was excluded in the determination of the TC_{05}. The TC_{05}s were calculated for these end-points by first fitting a multi stage model to the data. The multistage model is given by:

$$P(d) = 1 - e^{-q_0 - q_1 d - \ldots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, P(d) is the probability of the animal developing a tumour at dose d, and $q_i > 0$, i = 1,..., k are parameters to be estimated.

The models were fitted using GLOBAL82 (Howe & Crump, 1982), and a chi-square lack of fit test was performed for each model fit. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. The lower confidence limits presented are approximate, based on output from GLOBAL82. Results from the model fitting are displayed in Table A- 6. Plots of the data and the fitted models are shown in Figure A-2.

TC_{05}s were determined as the doses D (in mg/m^3) that satisfy

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

and then adjusted by multiplying by:

$$\frac{6\ h/day}{24\ h/day} \times \frac{5\ days/week}{7\ days/week} \times \frac{w\ weeks}{104\ weeks} \times \left\langle \frac{w\ weeks}{104\ weeks} \right\rangle^2$$

where, in the first term, which amortizes the dose to be constant over the lifetime of a mouse, w is the duration of the experiment (103 weeks). The second factor was suggested by Peto et al. (1984) and corrects for an experiment length that is unequal to the standard lifetime. Since tumours develop much more rapidly later in life, a greater than linear increase in the tumour rate is expected when animals are observed for tumours longer than their standard lifetime (or the reverse, when animals

are observed for a period shorter than their standard lifetime). (Application of this factor does not impact greatly on the final values, since it is very close to one.) The selected TC_{05} values for this study and their 95% lower confi dence limits (LCLs) are presented in Table A-6 and range from 2.3 mg/m^3 (95% LCL = 1.7 mg/m^3) or 1.1 ppm (95% LCL = 0.79 ppm) for Harderian gland tumours in males to 99 mg/m^3 (95% LCL = 23 mg/m^3) or 45 ppm (95% LCL = 10 ppm) for malignant lymphomas in males.

Table A-4: Parameter estimates and model deviances for each of four lagged-exposure models fitted to median cumulative exposure per person-year.

Model	Lag	Parameter estimates	Standard error	Deviance
1) RR = (1 + dose)^{alpha}	None	*alpha* = 0.2850	SE(*alpha*) = 0.0976	171.5
	2 years	*alpha* = 0.2852	SE(*alpha*) = 0.0982	171.6
	5 years	*alpha* = 0.2883	SE(*alpha*) = 0.0995	171.6
	10 years	*alpha* = 0.3064	SE(*alpha*) = 0.1034	171.1
	15 years	*alpha* = 0.2955	SE(*alpha*) = 0.1079	172.4
	20 years	*alpha* = 0.2891	SE(*alpha*) = 0.1141	173.6
	25 years	*alpha* = 0.2898	SE(*alpha*) = 0.1334	175.4
2) RR = 1 + *beta*•dose^{alpha}	None	*alpha* = 0.3999	SE(*alpha*) = 0.2733	172.0
		beta = 0.4557	SE(*beta*) = 0.8219	
	2 years	*alpha* = 0.3992	SE(*alpha*) = 0.2739	172.0
		beta = 0.4602	SE(*beta*) = 0.8279	
	5 years	*alpha* = 0.4024	SE(*alpha*) = 0.2737	172.0
		beta = 0.4647	SE(*beta*) = 0.8288	
	10 years	*alpha* = 0.4245	SE(*alpha*) = 0.2755	171.4
		beta = 0.4693	SE(*beta*) = 0.8345	
	15 years	*alpha* = 0.4835	SE(*alpha*) = 0.3397	172.6
		beta = 0.2878	SE(*beta*) = 0.5846	
	20 years	*alpha* = 0.4720	SE(*alpha*) = 0.3558	173.9
		beta = 0.3243	SE(*beta*) = 0.6572	
	25 years	*alpha* = 0.2960	SE(*alpha*) = 0.2833	175.3
		beta = 0.9293	SE(*beta*) = 1.5710	
3) RR = e$^{beta•dose}$	None	*beta* = 0.0029	SE(*beta*) = 0.0014	176.7
	2 years	*beta* = 0.0029	SE(*beta*) = 0.0015	176.8
	5 years	*beta* = 0.0031	SE(*beta*) = 0.0015	176.7
	10 years	*beta* = 0.0034	SE(*beta*) = 0.0016	176.4
	15 years	*beta* = 0.0035	SE(*beta*) = 0.0018	177.0

	20 years	*beta* = 0.0033	SE(*beta*) = 0.0022	178.2
	25 years	*beta* = 0.0033	SE(*beta*) = 0.0022	178.2
4) RR = 1 + *beta*•dose	None	*beta* = 0.0099	SE(*beta*) = 0.0065	174.7
	2 years	*beta* = 0.0102	SE(*beta*) = 0.0067	174.7
	5 years	*beta* = 0.0109	SE(*beta*) = 0.0072	174.6
	10 years	*beta* = 0.0137	SE(*beta*) = 0.0089	173.8
	15 years	*beta* = 0.0158	SE(*beta*) = 0.0106	174.1
	20 years	*beta* = 0.0179	SE(*beta*) = 0.0129	175.7
	25 years	*beta* = 0.0179	SE(*beta*) = 0.0129	175.7

Table A-6: Carcinogenic potency estimates (TC_{05}s)[a] of butadiene based on results of bioassays in experimental animals.

Tumour type	Males				
	TC_{05} (mg/m^3)	95% LCL (mg/m^3)	0^{2} [b]	df[c]	p[d]
Mice (from NTP, 1993)					
Alveolar/bronchiolar adenomas or carcinomas	2.4	1.4	1.0	3	0.79
Histiocytic sarcomas	12	8.4	7.6	5	0.18
Cardiac haemangiosarcomas	14	6.4	0.34	3	0.95
Forestomach squamous cell papillomas or carcinomas	29	13	6.1	3	0.11
Ovarian granulosa cell tumours	–	–	–	–	–
Mammary gland adenoacanthomas, carcinomas, or malignant mixed tumours	–	–	–	–	–
Hepatocellular adenomas or carcinomas	3.2	1.9	2.8	2	0.24
Harderian gland adenomas or carcinomas	2.3	1.7	0.5	2	0.77
Malignant lymphomas[e]	99	23	3.3	3	0.35
Rats (from Hazleton Laboratories Europe Ltd., 1981a)					
Mammary gland adenomas or carcinomas	–	–	–	–	–
Pancreatic exocrine adenomas	597	316	1.1	1	0.29
Leydig cell tumours	161	96	0	1	–
Thyroid follicular cell adenomas or carcinomas	–	–	–	–	–
Uterine sarcomas	–	–	–	–	–
Zymbal gland carcinomas	1023	905	1	1	0.32

Table A-6: (*continued*)

Tumour type	Females				
	TC_{05} (mg/m^3)	95% LCL (mg/m^3)	0^{2} [b]	df[c]	p[d]

Mice (from NTP, 1993)					
Alveolar/bronchiolar adenomas or carcinomas	5.2	3.2	9.1	4	0.06
Histiocytic sarcomas	21	12	5.4	4	0.25
Cardiac haemangiosarcomas	7.6	5.2	18	4	0.00
Forestomach squamous cell papillomas or carcinomas	14	8.1	4.3	4	0.36
Ovarian granulosa cell tumours	6.7	4.4	5.0	3	0.17
Mammary gland adenoacanthomas, carcinomas, or malignant mixed tumours	6.7	4.9	13	4	0.01
Hepatocellular adenomas or carcinomas	5.4	3.2	0.8	3	0.85
Harderian gland adenomas or carcinomas	4.7	2.7	1.5	2	0.47
Malignant lymphomas[e]	23	6.9	3.9	3	0.27
Rats (from Hazleton Laboratories Europe Ltd., 1981a)					
Mammary gland adenomas or carcinomas	6.7	4.7	0	0	–
Pancreatic exocrine adenomas	–	–	–	–	–
Leydig cell tumours	–	–	–	–	–
Thyroid follicular cell adenomas or carcinomas	142	113	0	1	–
Uterine sarcomas	189	113	0	0	–
Zymbal gland carcinomas	4872	766	0.06	2	0.97

[a] Values have been adjusted for lifetime exposure.

[b] Chi-squared goodness of fit statistic.

[c] Degrees of freedom.

[d] *p*-value of goodness of fit test (*p*-value < 0.05 indicates significant lack of fit).

[e] Values for malignant lymphomas presented here only for comparison; potency estimates for these tumours not considered relevant to humans due to the greater sensitivity of these mice to induction of this effect associated with the presence of an endogenous retrovirus.

Estimates of carcinogenic potency were also calculated based on the results of the bioassay in Sprague-Dawley rats (Hazleton Laboratories Europe Ltd., 1981a). In this study, rats were exposed to 0, 1000, or 8000 ppm (0, 2212, or 17 696 mg/m^3) for 6 h/day, 5 days/week, for 105 (males) or 111 (females) weeks. A high mortality rate was observed at the higher concentration; therefore, this exposure group was excluded from the analysis, except for the potency estimates for pancreatic exocrine adenomas in males (for this end-point, exclusion of the high-exposure group would have resulted in the exposure–response relationship curving downwards). As for mice, a multistage model was fit to the data for rats using GLOBAL82 and adjusted to account for study duration (w) by multiplying by:

$$\frac{6\ h/day}{24\ h/day} \times \frac{5\ days/week}{7\ days/week} \times \frac{wweeks}{104\ weeks} \times \left\langle \frac{wweeks}{104\ weeks} \right\rangle^2$$

where the duration of the experiment was 105 weeks for males and 111 weeks for females. The exposure–response curves and estimated adjusted TC_{05} values based on this study in rats are

presented in Figure A-3 and Table A-6, respectively. The concentrations of butadiene estimated to be associated with a 5% increased incidence of tumours ranged from 6.7 mg/m^3 (95% LCL = 4.7 mg/m^3) or 3.0 ppm (95% LCL = 2.1 ppm) to 4872 mg/m^3 (95% LCL = 766 mg/m^3) or 2203 ppm (95% LCL = 346 ppm) for tumours of the mammary gland and Zymbal gland in female rats, respectively. Although the available data for analysis of exposure–response were more limited for rats than for mice, it is interesting to note the similarity in estimates of potency for mammary gland tumours (i.e., 6.7 mg/m^3 in both species).

Table A-5: Model validation *p*-values for Delzell et al. (1995) study.

	Proportion of *p*-values[a] that are		
Model	**less than 0.01**	**less than 0.05**	**less than 0.1**
1) RR = (1 + dose)^{alpha}	0.074	0.167	0.252
2) RR = 1 + *beta*•dose^{alpha}	0.084	0.19	0.286
3) RR = e$^{beta \cdot dose}$	0.08	0.188	0.264
4) RR = 1 + *beta*•dose	0.103	0.214	0.303

[a] *p*-value of likelihood ratio test of equality of parameters fitted to each half of the data.

Based on modelling (using THC; Howe, 1995a) of the inci dence of micronucleated polychromatic erythrocytes in B6C3F$_1$ mice exposed to butadiene for up to 15 months in the NTP bio assay, BMC$_{05}$s for somatic cell mutations were very similar to the lower end of the range of the TC$_{05}$s for tumour induction.

Benchmark concentrations for ovarian atrophy in mice

Benchmark concentrations (BMC$_{05}$s) for ovarian atrophy were derived on the basis of the chronic bioassay conducted by the NTP (1993) in which B6C3F$_1$ mice were exposed to concentrations of 0, 6.25, 20, 62.5, 200, or 625 ppm (0, 13.8, 44.2, 138, 442, and 1383 mg/m^3) butadiene for up to 2 years. There was a concentra tion-related increase in the incidence as well as the severity of ovarian atrophy, as summarized in Table A-7.

The exposure–response relationship for ovarian atrophy from this study was quantified by fitting the following model to the dose–response data (Howe, 1995b):

$$P(d) = \begin{cases} q_0 & \text{if } d \le d_0 \\ q_0 + (1 - q_0) \cdot \left[1 - e^{-q_1 (d - d_0) - \ldots - q_k (d - d_0)^k} \right] & \text{if } d \le d_0 \end{cases}$$

where d is dose, k is the number of dose groups in the study minus one, P(d) is the probability of the animal developing the effect at dose d, and $q_i > 0$, $i = 1, \ldots, k$ and d_0 are parameters to be estimated. The models were fit using THRESH (Howe, 1995b), and the BMC$_{05}$s were calculated as the dose D that satisfies:

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit.

The BMC_{05} was then amortized to be constant over the standard life of a mouse by multiplying by:

$$\frac{6\ h/day}{24\ h/day} \times \frac{5\ days/week}{7\ days/week}$$

Resulting BMC_{05}s and lack of fit information for all models fit are displayed in Table A-8.

The model fitted to all six exposure groups exhibited a significant lack of fit, likely due to the fact that the curve rises sharply and then plateaus at the three highest exposure groups. Plots of the data and fitted model are displayed in Figure A-4. Since a good fit in the range of the BMC_{05} (in the vicinity of 6.25 ppm [13.8 mg/m^3]) is desired, the model was refitted omitting the two highest exposure groups. This model again indicates a marginal lack of fit. The graph of this model (Figure A-5) indicates that this model provides a reasonable visual fit to the data, but the resulting BMC_{05} is uncertain due to lack of fit of the model.

The BMC_{05} for the model excluding the two highest dose groups was calculated to be 0.57 mg/m^3, with a 95% LCL of 0.44 mg/m^3.

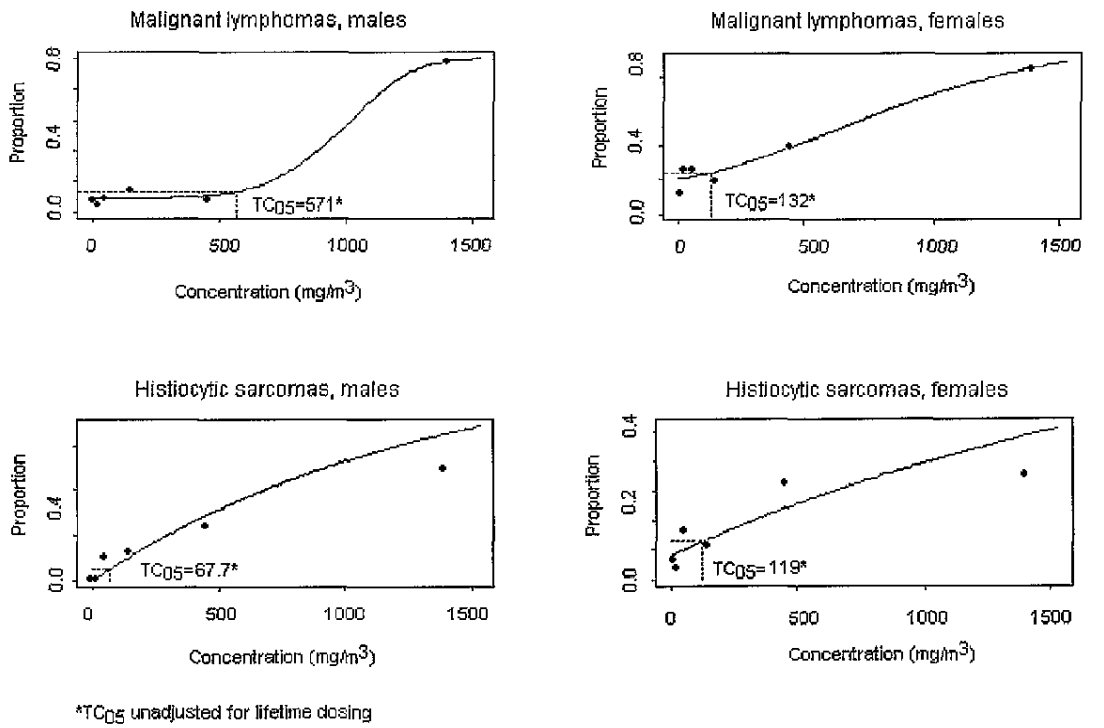
If only those animals that had moderate or marked ovarian atrophy from all exposure groups were included, the resulting BMC_{05} would be 9.6 mg/m^3 (95% LCL = 7.6 mg/m^3), although there is again a significant lack of fit (Figure A-6). If the highest exposure group is excluded, the BMC_{05} for moderate or marked ovarian atrophy becomes 3.1 mg/m^3, with a 95% LCL of 2.5 mg/m^3 (Figure A-7).

Table A-7: Incidence and severity of ovarian atrophy observed in 2-year bioassay in mice (NTP, 1993).

Exposure level (ppm)	Number of animals examined	All severities	Minimal severity	Mild severity	Moderate severity	Marked severity
0	49	4	1	2	1	0
6.25	49	19	0	15	4	0
20	48	32	1	23	8	0
62.5	50	42	3	18	21	0
200	50	43	0	9	34	0
625	79	69	0	19	47	3

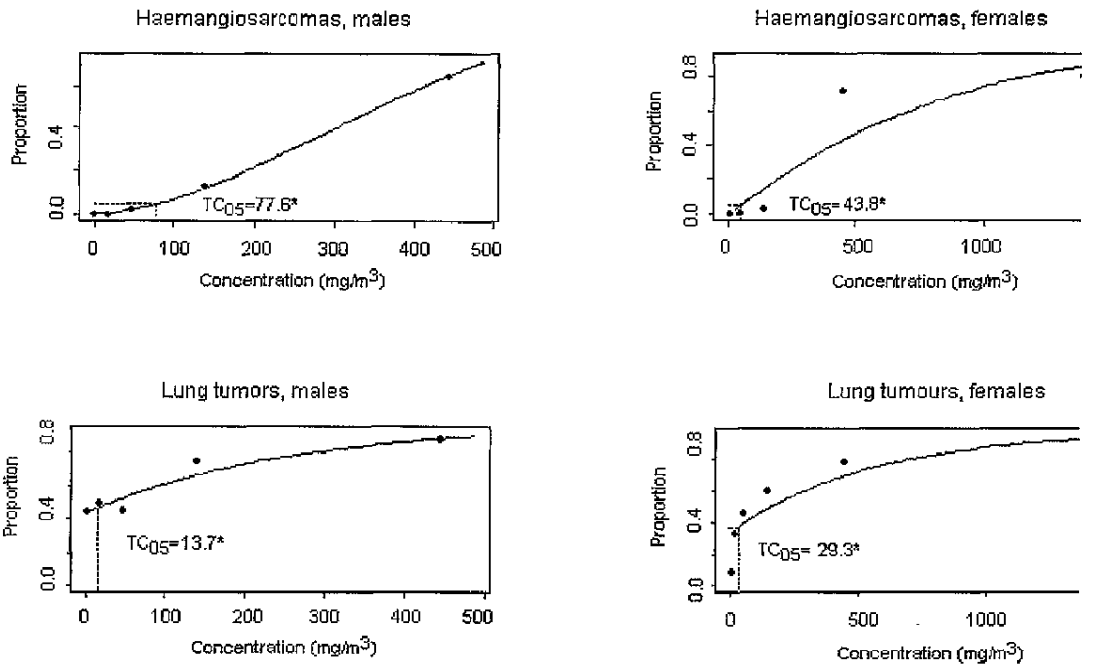
Table A-8: Benchmark concentrations for ovarian atrophy.

Ovarian atrophy	BMC_{05} (ppm)	95% LCL on BMC_{05} (ppm)	BMC_{05} (mg/m^3)	95% LCL on BMC_{05} (mg/m^3)	Chi-square	df	*p*-value
All severities	2.5	1.9	5.6	4.1	61	4	0.00
All severities, excluding top two dose groups	0.25	0.20	0.57	0.44	7.0	2	0.03
Moderate/marked severity	4.3	3.4	9.6	7.6	37.1	4	0.00
Moderate/marked severity, excluding top dose group	1.4	1.1	3.1	2.5	2.2	3	0.55



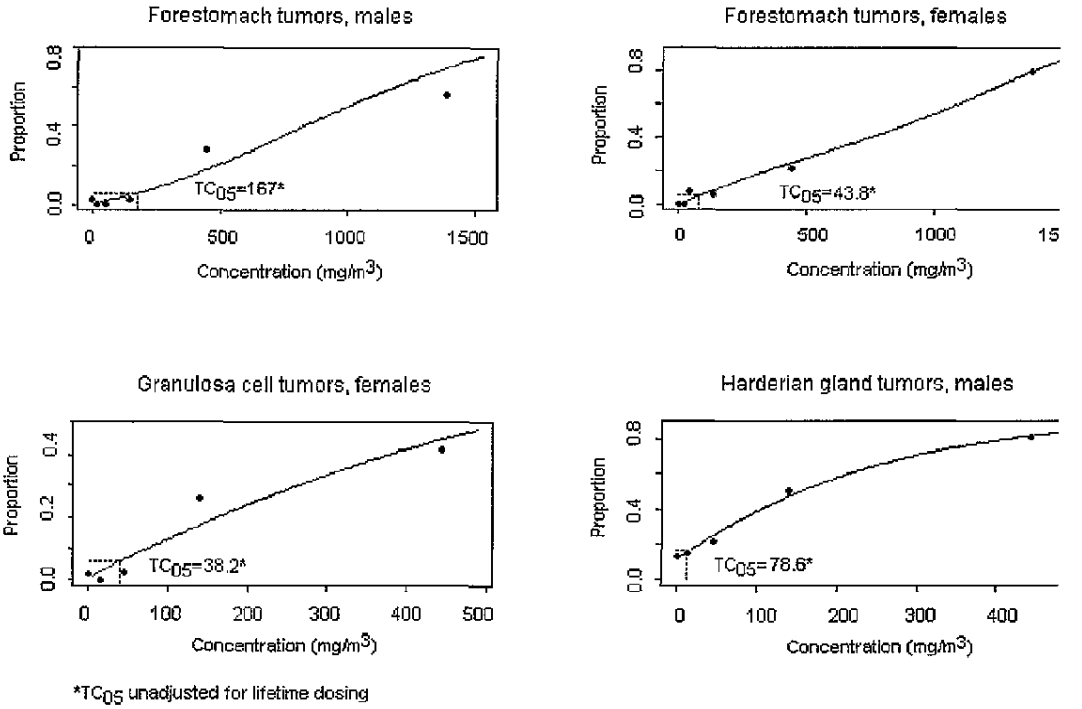
*TC_{05} unadjusted for lifetime dosing

Figure A-2: Exposure-response analysis for butadiene-induced tumours in mice.



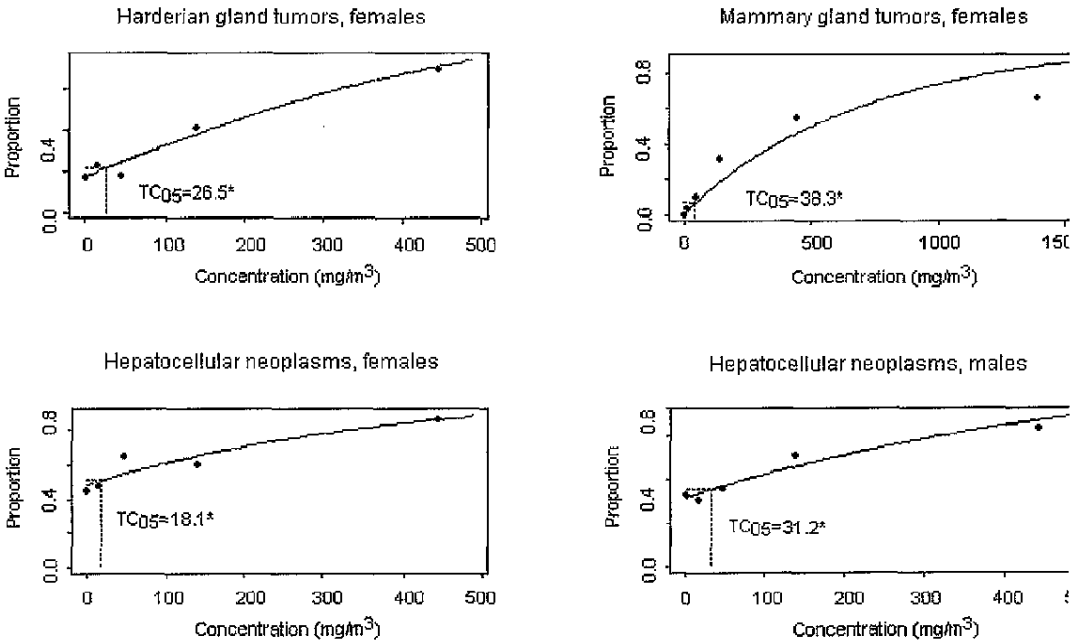
*TC_{05} unadjusted for lifetime dosing

Figure A-2 (continued)



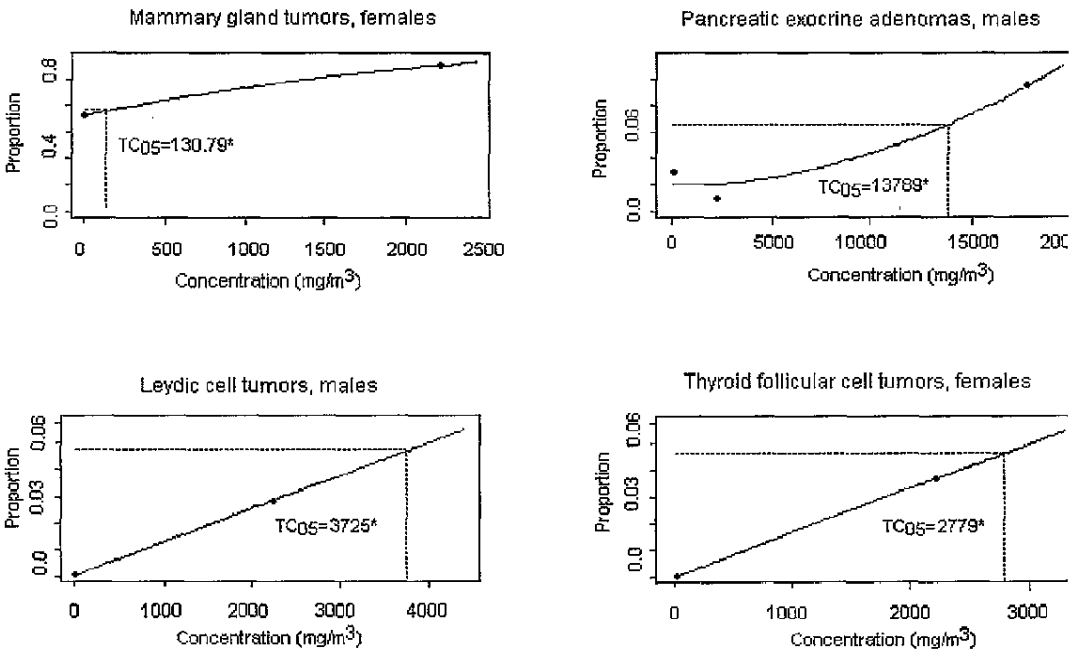
*TC_{05} unadjusted for lifetime dosing

Figure A-2 (continued)



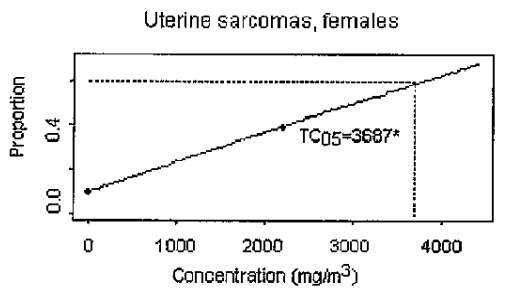
*TC_{05} unadjusted for lifetime dosing

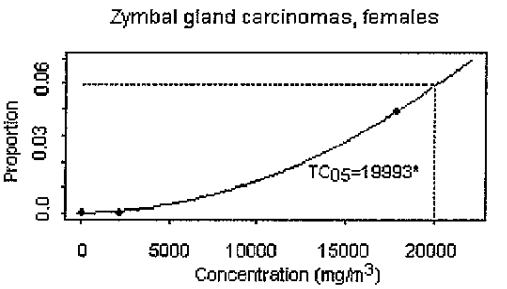
Figure A-2 (continued)

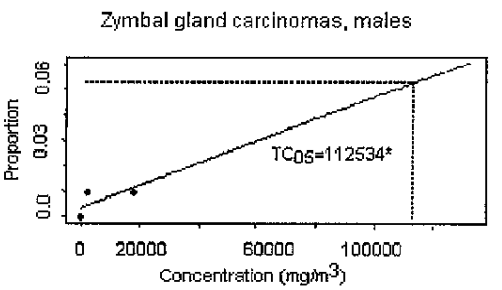


*TC_{05} unadjusted for lifetime dosing

Figure A-3: Exposure-response analysis for butadiene-induced tumours in rats.







*TC_{05} unadjusted for lifetime dosing

Figure A-3 (continued)

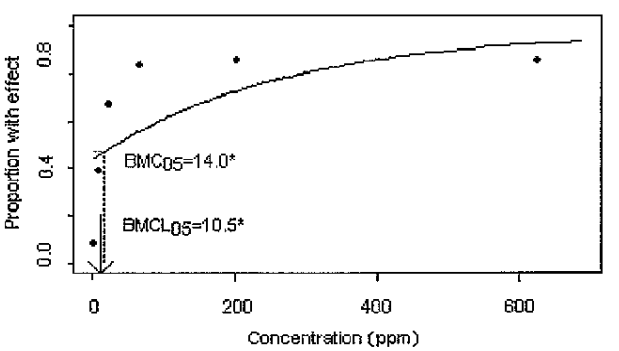


Figure A-4: Exposure-response analysis for ovarian atrophy in mice (*BMC_{05} and $BMCL_{05}$ unadjusted for lifetime dosing).

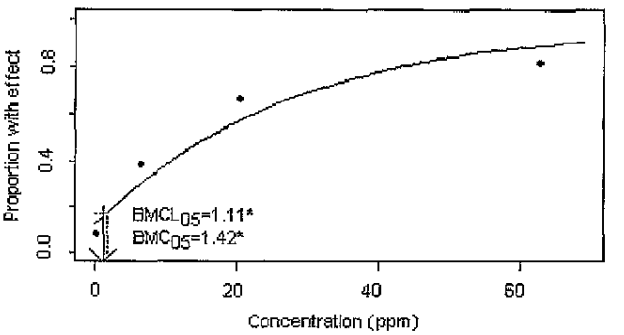


Figure A-5: Exposure-response analysis for ovarian atrophy in mice excluding two highest dose groups
(* BMC_{05} and $BMCL_{05}$ unadjusted for lifetime dosing).

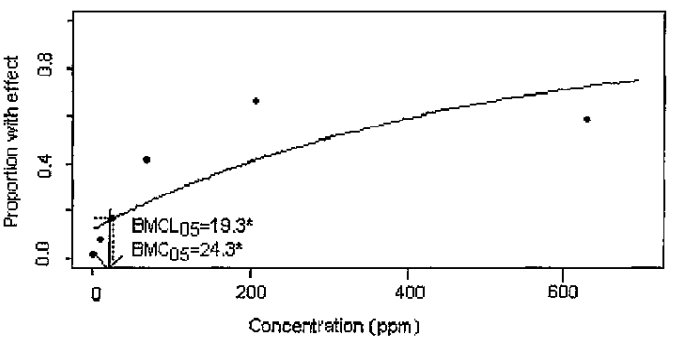


Figure A-6: Exposure-response analysis for moderate/marked ovarian atrophy
(*BMC05 and BMCL05 unadjusted for lifetime dosing).

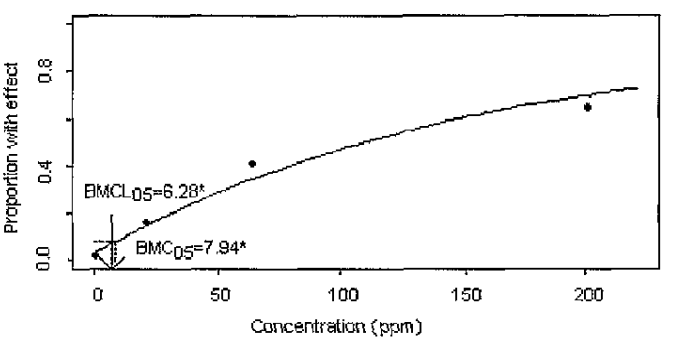


Figure A-7: Exposure-response for moderate/marked ovarian atrophy, excluding high-dose group
(*BMC_{05} and $BMCL_{05}$ unadjusted for lifetime dosing).

INTERNATIONAL CHEMICAL SAFETY CARD

1,3-BUTADIENE ICSC:0017

RÉSUMÉ D'ORIENTATION

Ce CICAD sur le 1,3-butadiène a été préparé par la Direction de l'Hygiène de l'Environnement de Santé Canada sur la base d'une documentation préparée simultanément dans le cadre du Programme d'évaluation des substances prioritaires, en application de la Loi canadienne sur la protection de l'environnement (LCPE). Les évaluations sanitaires des substances prioritaires effectuées en application de cette loi portent sur les effets potentiels que ces produits pourraient avoir sur la santé humaine en cas d'exposition indirecte dans l'environnement général. Cette mise au point prend en compte des données allant jusqu'à fin avril 1998. L'appendice 1 donne des informations sur la nature de l'examen par des pairs ainsi que sur les sources documentaires utilisées. Des renseignements sur l'examen de ce CICAD par des pairs sont donnés à l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui s'est tenue à Helsinki (Finlande) du 26 au 29 juin 2000. La liste des participants à cette réunion figure à l'appendice 3. La fiche internationale sur la sécurité chimique (ICSC 0017) du 1,3-butadiène, établie par le Programme international sur la sécurité chimique (IPCS, 1993) est également reproduite dans le présent document.

Le 1,3-butadiène (No CAS 106-99-0) résulte de la combustion incomplète de certains produits lors de processus naturels ou d'activités humaines. C'est également un produit chimique industriel principalement utilisé pour la préparation de polymères, notamment du polybutadiène et des caoutchoucs et latex styrène- butadiène ou des élastomères acrylonitrile-butadiène. Le 1,3-butadiène pénètre dans l'environnement avec les gaz d'échappement des véhicules à essence ou à gazole, lors de l'utilisation de combustibles à d'autres fins que le transport, de la combustion de la biomasse ou encore lors de son utilisation sur des sites industriels.

Le 1,3-butadiène ne persiste pas dans l'environne ment mais il est néanmoins répandu dans tout le milieu urbain du fait de la présence généralisée des sources de combustion où il prend naissance. C'est dans les villes et à proximité immédiate des installations industrielles que sont mesurées les concentrations atmosphériques les plus fortes.

L'exposition de la population générale au 1,3- butadiène est due principalement à sa présence dans l'air extérieur ou intérieur. Comparativement, la contribution des autres véhicules, comme les aliments ou l'eau de boisson, reste négligeable. En revanche, celle de la fumée de tabac peut être importante.

Le métabolisme du 1,3-butadiène se révèle être de même nature d'une espèce à l'autre, mais il y a néan moins des différences quantitatives notamment en ce qui concerne la proportion de métabolites présumés toxiques qui se forment; ainsi chez la souris le métabolisme oxydatif en mono-, puis en diépoxyde est plus important que chez le rat ou l'Homme. Par ailleurs, il peut égale ment y avoir des variations interindividuelles dans la capacicité de métabolisation chez l'Homme, variations qui s'expliquent par le polymorphisme génétique des enzymes en cause.

Le 1,3-butadiène présente une faible toxicité aiguë chez les animaux de laboratoire. On a toutefois observé une atrophie ovarienne à toutes les concentrations chez des souris exposées à ce composé pendant une période prolongée. D'autres effets sur les ovaires ont également été relevés lors d'études à court terme. Chez les souris mâles, on a constaté que le 1,3-butadiène provoquait une atrophie testiculaire, mais à des concentrations supéri eures à celles qui étaient toxiques pour les femelles. Les données limitées dont on dispose ne permettent pas de conclure que ce composé est tératogène pour la progéni ture des animaux de laboratoire mâles ou femelles qui y ont été exposés, ni qu'il est véritablement toxique pour le foetus à des concentrations inférieures à celles qui sont toxiques pour la mère.

Le 1,3-butadiène exerce également divers effets sur le sang et la moelle osseuse de la souris; en ce qui con cerne le rat, les données, bien que limitées, ne mettent pas en évidence d'effets de ce genre.

L'ensemble des études montre qu'une fois inhalé, le 1,3-butadiène se révèle fortement cancérogène chez la souris, provoquant des tumeurs de localisations multiples à toutes concentrations. Il se révèle également cancéro gène chez le rat à toutes les concentrations, selon la seule étude adéquate dont on dispose. Chez cette espèce, les seules concentrations étudiées étaient beaucoup plus fortes que pour la souris, mais il apparaît néanmoins que le rat est l'espèce la moins sensible, si l'on prend comme élément de comparaison l'incidence des tumeurs. Il est probable que la plus grande sensibilité observée chez les souris est liée aux différences interspécifiques mention nées plus haut concernant le métabolisme, et notamment le métabolisme qui conduit à la formation d'époxydes actifs.

Le 1,3-butadiène a une action mutagène sur les cellules somatiques de la souris et du rat, avec une activité plus forte chez la souris. On a également constaté d'autres lésions génétiques dans les cellules somatiques de cette dernière espèce, à l'exclusion de celles du rat. Le composé s'est révélé systématiquement génotoxique pour les cellules germinales de la souris, mais apparemment pas pour celles du rat, selon la seule étude retrouvée.

Toutefois il n'y a apparemment pas de différence interspécifique pour ce qui est de la sensibilité aux effets génétiques dus aux époxydes résultant de la métabolisa tion du 1,3-butadiène. Selon certaines données con cernant l'exposition professionnelle mais qui restent toutefois limitées, le 1,3-butadiène serait également génotoxique pour l'Homme et provoquerait des lésions mutagènes et clastogènes dans les cellules somatiques.

Il existe, entre l'exposition au 1,3-butadiène sur le lieu de travail et certaines leucémies, une corrélation qui répond à plusieurs des critères d'une relation de cause à effet. L'étude la plus vaste et la plus exhaustive effectuée jusqu'ici, et qui a porté sur une cohorte de travailleurs employés dans de multiples usines, a mis en évidence un parallélisme entre une augmentation constatée de la mortalité par leucémie et l'exposition cumulée estimative au 1,3-butadiène dans les industries produisant des élastomères styrène-butadiène. La correction pour tenir compte de l'exposition au benzène et au styrène n'a pas fait disparaître cette corrélation, qui se manifestait d'ailleurs le plus fortement dans les sous-groupes potentiellement les plus exposés. On a également observé une corrélation entre l'exposition au 1,3- butadiène et les leucémies lors d'une étude cas-témoins menée indépendamment de l'enquête précitée sur une population de travailleurs en grande partie identique. Par contre, on n'a pas constaté d'augmentation de la mortalité par leucémie chez des travailleurs employés à la production de butadiène monomère mais non exposés simultanément à certaines des autres substances présentes dans l'industrie des élastomères styrène- butadiène, en dépit d'éléments d'appréciation limités concernant la possibilité d'une association avec la mortalité par lymphosarcomes ou réticulosarcomes dans certains sous-groupes.

Au vu des données épidémiologiques et toxicolo giques, le 1,3-butadiène est cancérogène pour l'Homme et pourrait également être génotoxique. Le pouvoir cancérogène (concentration qui entraîne une augmen tation de 1% de la mortalité par leucémie) a été évalué à 1,7 mg/m^3 en s'appuyant sur les résultats de l'enquête épidémiologique la plus vaste et la mieux conduite sur des travailleurs exposés. Cette valeur correspond à l'extrémité inférieure de la série de concentrations tumorigènes déterminée par des études sur des rongeurs. Le 1,3-butadiène présente également une toxicité génésique chez les animaux de laboratoire. Ce potentiel toxique peut s'évaluer par la concentration de référence de 1,3-butadiène obtenue dans le cas des effets ovariens et qui est égale à 0,57 mg/m^3.

Les effets sanitaires du 1,3-butadiène et le mode d'action de ce composé ont été étudiés en détail, mais d'importants travaux de recherche continuent de lui être consacrés afin de tenter de lever les incertitudes qui subsistent dans la base de données.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre el 1,3-butadieno, preparado por la Dirección General de Higiene del Medio del Minis terio de Salud del Canadá, se basó en la documentación preparada al mismo tiempo como parte del Programa de Sustancias Prioritarias en el marco de la Ley Canadiense de Protección del Medio Ambiente (CEPA). El objetivo de las evaluaciones sanitarias de las sustancias priori tarias en el marco de la CEPA es valorar los efectos potenciales de la exposición indirecta en el medio ambiente general para la salud humana. En este examen se utilizaron los datos obtenidos hasta el final de abril de 1998. La información relativa al carácter del examen colegiado y a la disponibilidad del documento original se presenta en el apéndice 1. La información sobre el examen colegiado de este CICAD figura en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final, celebrada en Helsinki (Finlandia) del 26 al 29 de junio de 2000. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0017) para el 1,3-butadieno, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El 1,3-butadieno (CAS N° 106-99-0) se produce por una combustión incompleta en procesos naturales y actividades humanas. Es también un producto químico industrial que se utiliza fundamentalmente en la producción de polímeros, en particular polibutadieno, cauchos y látex de estireno-butadieno y cauchos de nitrilo-butadieno. El 1,3-butadieno se incorpora al medio ambiente a partir de las emisiones de los gases de escape de los vehículos con motor de gasolina y diésel, de la combustión de combustibles fósiles no utilizados en el transporte, de la combustión de biomasa y de usos industriales sobre el terreno.

El 1,3-butadieno no es persistente, pero sí ubicuo en el medio ambiente urbano, debido a la presencia generalizada de sus fuentes de combustión. Las concentraciones atmosféricas más altas se han medido en el aire de las ciudades y en las cercanías de fuentes industriales.

La población general está expuesta al 1,3-buta dieno fundamentalmente mediante el aire del ambiente y de los espacios cerrados. En comparación, otros medios, entre ellos los alimentos y el agua de bebida, contrib uyen de manera insignificante a la exposición a él. El humo del tabaco puede producir cantidades significa tivas de 1,3-butadieno.

El metabolismo del 1,3-butadieno parece ser cualitativamente semejante en todas las especies, aunque hay diferencias cuantitativas en los metabolitos supues tamente tóxicos que se forman; los ratones parecen oxidar el 1,3-butadieno a monoepóxido y después a diepóxido en mayor medida que las ratas o las personas. Sin embargo, la capacidad metabólica para el 1,3- butadieno puede variar de unas personas a otras, en función del polimorfismo genético de las enzimas correspondientes.

El 1,3-butadieno tiene una toxicidad aguda baja en animales experimentales. Sin embargo, la exposición prolongada de ratones a este producto se asoció con la aparición de atrofia ovárica con todas las concentra ciones utilizadas en los ensayos. En estudios de expo sición más breve se observaron también efectos en los ovarios. En los ratones machos se detectó asimismo atrofia testicular a concentraciones superiores a las asociadas con efectos en las hembras. Sobre la base de los limitados datos disponibles, no hay pruebas conclu yentes de que el 1,3-butadieno sea teratogénico en los animales experimentales tras la exposición materna o paterna o de que induzca una toxicidad fetal importante a concentraciones inferiores a las que provocan toxici dad materna.

El 1,3-butadieno indujo también diversos efectos en la sangre y en la médula ósea de ratones; aunque los datos son limitados, no se han observado efectos seme jantes en las ratas.

El 1,3-butadieno inhalado es un potente carcinó geno en ratones, induciendo tumores en lugares múltiples a todas las concentraciones utilizadas en todos los estudios identificados. Fue también carcinogénico en ratas a todos los niveles de exposición en el único estudio disponible al respecto; aunque en las ratas sólo se ensayaron concentraciones mucho más altas que en los ratones, las ratas parecen ser la especie menos sensible, tomando como base la comparación de los datos sobre la

incidencia de tumores. La mayor sensibilidad de los ratones que las ratas a la inducción de estos efectos por el 1,3-butadieno probablemente se debe a diferencias entre las especies con respecto al metabolismo de formación de epóxidos activos.

El 1,3-butadieno es mutagénico en células somáticas tanto de ratones como de ratas, aunque la potencia mutagénica fue mayor en los primeros. De la misma manera, el 1,3-butadieno indujo otros daños genéticos en células somáticas de ratones, pero no en las de ratas. Fue también sistemáticamente genotóxico en células germinales de ratones, pero no en la única valoración identificada en ratas. Sin embargo, no se observaron diferencias aparentes en la sensibilidad de las especies a los efectos genéticos inducidos por los metabolitos epóxidos del 1,3-butadieno. Hay también pruebas limitadas de poblaciones expuestas en el lugar de trabajo de que el 1,3-butadieno es genotóxico para las personas, induciendo daños mutagénicos y clastogénicos en las células somáticas.

La asociación entre la exposición al 1,3-butadieno en el entorno de trabajo y la leucemia cumple varios de los criterios tradicionalmente establecidos para la causalidad. En el estudio más amplio y completo realizado hasta el momento, utilizando una cohorte de trabajadores de diversas instalaciones, la mortalidad por leucemia aumentó con una exposición acumulativa estimada al 1,3-butadieno en la industria del caucho de estireno-butadieno; esta asociación se mantuvo tras el control de la exposición al estireno y al benceno y alcanzó la intensidad máxima en los subgrupos con el mayor potencial de exposición. Análogamente, en un estudio de casos y testigos independiente basado prác ticamente en la misma población de trabajadores se observó una asociación entre la exposición al 1,3-buta dieno y la leucemia. Sin embargo, no se produjo un aumento de la mortalidad a causa de la leucemia en los trabajadores de la producción de monómeros de buta dieno que no estaban simultáneamente expuestos a algunas de las otras sustancias presentes en la industria del caucho de estireno-butadieno, aunque en algunos subgrupos se obtuvieron pruebas limitadas de asociación con la mortalidad por linfosarcoma y reticulosarcoma.

Los datos epidemiológicos y toxicológicos dispon ibles demuestran que el 1,3-butadieno es carcinogénico, y también puede ser genotóxico, para las personas. Se calculó una potencia carcinogénica (concentración que produce un aumento del 1% de la mortalidad por leu cemia) de 1,7 mg/m^3, sobre la base de los resultados de la mayor investigación epidemiológica bien realizada en trabajadores expuestos. Este valor es semejante al nivel más bajo de la gama de concentraciones tumorígenas determinadas a partir de los estudios realizados con roedores. El 1,3-butadieno indujo también toxicidad reproductiva en animales experimentales. Como medida de su potencia para inducir efectos reproductivos, se obtuvo una concentración de referencia de 0,57 mg/m^3 para la toxicidad ovárica en los ratones.

Aunque se han investigado a fondo los efectos en la salud asociados con la exposición al 1,3-butadieno y el mecanismo de acción para la inducción de estos efectos, se siguen realizando numerosas investigaciones sobre esta sustancia, a fin de tratar de abordar algunas de las incertidumbres asociadas con la base de datos.

FOOTNOTES

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

[2] Personal communication from L.A. Graham, River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, 1996.

[3] Hazardous Substances Databank, National Library of Medicine's TOXNET system, searched 10 December 1999.

[4] Unpublished data on butadiene levels in Canada from National Air Pollution Surveillance program, provided by T. Dann, River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, April 1997.

[5] Also letter dated 28 August 1996 from P. Steer, Science and Technology Branch, Ontario Ministry of Environment and Energy, to J. Sealy, Health Canada, re. 1,3-butadiene and chloroform data (File No. 1E080149.MEM).

[6] Personal communication from H. Michelin, Bayer Inc., Sarnia, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, 1997.

[7] Also personal communication dated 24 December 1997 from X.-L. Cao to Health Canada, re. method detection limits for 24-h air samples from multimedia exposure pilot study (File No. MDL.XLS).

[8] Personal communication from R. Cooper, Department of Biomedical and Environmental Health, School of Public Health, University of California, Berkeley, California, 1989 (cited in CARB, 1992).

[9] Also personal communication (correspondence dated 25 March 1998) from J.A. Swenberg, University of North Carolina, Chapel Hill, NC, to Health Canada.

[10] The terminology for cancers of the lymphohaematopoietic system is that used by authors of the individual study accounts.

[11] SMRs are presented here in the format used by the authors; i.e., SMR = observed/expected or SMR = observed/expected × 100.

[12] It is not possible to determine, with any certainty, the size of the population in these earlier studies that was not subsumed in the later investigation by Delzell et al. (1995). One of the small plants of approximately 600 workers included in the Matanoski et al. (1990, 1993) cohort was not examined by Delzell et al. (1995).

[13] Also personal communication (letter dated 17 October 1997) from J.B. Ward, Jr., Division of Environmental Toxicology, Department of Preventative Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, to Health Canada.

[14] Personal communication (electronic correspondence dated 15 November 1997) from J.B. Ward, Jr., Division of Environ mental Toxicology, Department of Preventative Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, to Health Canada.

[15] Also personal communications (letter dated 17 October 1997 and electronic correspondence dated 15 November 1997) from J.B. Ward, Jr., Division of Environmental Toxicology, Department of Preventative Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, to Health Canada.

[16] Also personal communication (correspondence dated 30 March 1998) from R.D. Irons, University of Colorado Health Sciences Center, Denver, CO, to Health Canada.

[17] Personal communication (electronic correspondence dated 26 June 1998) from B. Davis, National Institute for Environmen tal Health and Safety, National Toxicology Program, Research Triangle Park, NC, to Health Canada.

[18] The potency estimate for carcinogenicity is determined by calculating the dose or concentration associated with an increase in cancer incidence or mortality of an appropriate percentage. When based on toxicological data from studies in experimental animals, a 5% increase is generally chosen, as these values usually lie within or close to the observable range (i.e., a TC_{05} is calculated). When epidemiological data form the basis for derivation of a tumorigenic concentration, the percent increase selected is that which falls within the area of the exposure–response curve that represents the majority of the observable data; this is often less than 5%. In the case of butadiene, the carcinogenic potency calculated on the basis of modelling of epidemiological data (as described herein) was considered to be best defined as a 1% increase in mortality due to leukaemia (i.e., a TC_{01}).

[19] Similar to tumorigenic concentrations (TC_{05}s), benchmark concentrations for non-cancer effects (or BMC_{05}s), when based on data in experimental animals, represent the dose or concen tration associated with a 5% increase in the incidence of an effect compared with controls.

[20] Unpublished data on butadiene levels in Canada from National Air Pollution Surveillance program, provided by T. Dann, River Road Environmental Technology Centre, Environment Canada, Ottawa, Ontario, to Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec, April 1997.

[21] Although it has not been possible to quantitatively character ize uncertainty regarding these estimates of exposure and the impact of this uncertainty upon the estimates of carcinogenic potency, data being collected currently may permit a more quantitative characterization in future (personal communica tion [correspondence dated 20 March 1998] from J. Lynch, Consultant, Rumson, NJ, to Health Canada).

[22] The cooperation of the sponsors and researchers for the Delzell et al. (1995) study in the provision of these data is gratefully acknowledged.

[23] Epicure is a collection of interactive programs used to fit models to epidemiological data. The specific program used to model the data for this cohort of styrene-butadiene rubber workers is called AMFIT, which is specially designed to model hazard functions for censored cohort survival data. The strength of Epicure lies in its ability to easily allow the background rate to depend on user-specified strata, such as age, calendar period, and race.

[24] Mortality data were provided to Health Canada by Statistics Canada. The cooperation of the registrars of vital statistics in the provinces and territories of Canada who make mortality data available to Statistics Canada under federal–provincial agreements is gratefully acknowledged.

See Also:
Toxicological Abbreviations
Butadiene, 1,3- (ICSC)